

Epidemiology and Natural History of Oral Human Papillomavirus Infections: A Review

By: Leigha D. Rock, RDH, DipDH, BSc, MSc (candidate)^{1,2}

Jade Lavallee, RDH, DipDH, BSc, MSc (candidate)^{1,2}

Miriam P. Rosin, BSc, PhD^{1,3}

March 20, 2015

1. British Columbia Cancer Agency Research Centre, Cancer Control Research, Vancouver, British Columbia
2. Faculty of Dentistry, University of British Columbia, Vancouver, British Columbia
3. Faculty of Biomedical Physiology and Kinesiology, Simon Fraser University, Burnaby, British Columbia

ABSTRACT

The aim of this literature review is to explore current findings relating to the natural history of the acquisition and persistence of oral human papillomavirus (HPV) infection, as well as to identify the risk factors and populations at risk associated with oral HPV infections. The impact and potential implications of HPV vaccination on HPV-associated head and neck cancer will also be discussed. A detailed search of electronic databases was conducted; inclusion criteria limited the findings to primary studies conducted within the past eight years. Findings confirm that oral HPV infection is recognized as a cause of a distinct subset of oropharyngeal cancer (OPC) that is rising drastically in incidence, and presents with non-traditional risk factors. The prevalence of oral HPV infection in the general population ranges from 1.8-7.3%. Increased persistence of high-risk HPV infection is linked to increased risk of malignancy. Findings from the literature outlined emerging risk factors such as biological sex, tobacco, high-risk sexual behavior, and immunosuppression. While the etiology and natural history of oral HPV infection are still being understood, vaccination efforts appear to be producing positive results. Further research is needed to investigate the natural history of oral HPV infection and HPV-positive OPC.

INTRODUCTION

Head and neck squamous cell carcinoma (HNSCC) is the 6th most common cancer in the world. (48) In the United States, oral cavity cancer (OCC) and oropharyngeal cancer (OPC) are the eighth most common cancers among men and the 14th most common among women. (49) Oropharyngeal cancers include those arising in the soft palate, uvula, tonsils, posterior pharyngeal walls, and base of the tongue: oral cavity cancers include the floor of the mouth, mobile portions of the tongue, and cheeks. (34) There has been a steady increase in the proportion of HPV-positive OPC. From 1998 to 2004, the incidence of HPV-positive OPC increased by 225% while incidence of HPV-negative cancers declined by half. (17) A Turkish study also demonstrated an increase in the proportion of HPV-positive OPC (from 33% to 70%) between 1996 and 2011. (96) OPCs are predicted to surpass cervical cancer by 2020. (17) Tobacco and alcohol are known risk factors for HNSCC. Recently, human papillomavirus (HPV) has been recognized as an etiological factor for the development of OPCs, particularly those arising in the tonsils and the base of the tongue. (10, 26, 35) HPV strains are categorized as being either high-risk (oncogenic) strains associated with malignancies or low-risk (non-oncogenic) strains associated with benign diseases. HPV-16 is the most prevalent high-risk genotype and accounts for 71 – 95% of HPV-positive OPCs. (55, 57, 69, 81, 87, 96) Epidemiological data indicates that although the incidence of OCC is declining, the incidence of OPC is increasing, particularly in men. Chaturvedi *et al.* (16, 17) found that HPV-positive OPC increased 3-fold in the three decades between 1970 and 2000 (23% to 68% respectively) (16, 17, 26, 79), and other studies have

found similar trends. (26, 79) It has been suggested that if this trend continues, the yearly incidence of HPV-positive OPC could surpass that of cervical cancer by 2020.

(17)

Twenty to 30% of patients with OPC do not present with traditional risk factors. (70) There is an urgent need to identify the risk factors and the populations at risk for this disease. Once the risk factors for OPC have been ascertained, these populations could be assessed to determine if screening or other preventive measures could be effective. At present, it is unclear if the natural history, risk factors and at-risk populations for persistent oral HPV infection, differ from those previously identified for anogenital HPV infection. There is a growing body of literature that aims to establish the natural history and risk factors associated with high-risk oral HPV infection and HPV-positive OPC. The purpose of this literature review is to review the current understanding of the portion of the natural history of oral HPV infection pertaining to the acquisition of oral HPV infection, and to identify the recognized risk factors and populations at risk of high-risk oral HPV infection (Figure 1). Risk factors surrounding the persistence of high-risk oral HPV infection and HPV-positive OPC will be explored in depth. Finally, the potential implications of HPV vaccination on HPV associated HNSCC will be discussed.

METHODS

A detailed search of electronic databases was conducted including PubMed, MEDLINE, CINAHL, Web of Science, EBSCO and Ovid. The keywords used for searching included: “natural history”; “human papillomavirus”; “oropharyngeal

cancer”; “squamous cell carcinoma”; “anal cancer”; “risk factors”; “concordance”; “HIV”; “oral sex”; “high risk sex”. The references and bibliographies of related studies were also scrutinized.

The inclusion criteria for this literature review consisted of peer-reviewed primary studies, current to within the last eight years (2006), and pertaining to the natural history and risk factors for oral HPV infection and HPV-positive OPC. Secondary publications, such as expert opinion articles and literature reviews, were considered for background information.

DISCUSSION

Natural History

A pre-existing framework for cervical cytological screening (Papanicolaou test) supported initial studies examining the natural history of cervical HPV. Consequently, cervical cancer became the primary example of natural history for HPV-caused cancer. The causal relationship between high-risk HPV infection and cervical cancer, particularly its presumed progression from high-grade cervical intraepithelial neoplasia (CIN) to invasive cancer is quite clear (Figure 2). (46) Anal cancer resembles cervical cancer more than the other anogenital cancers with respect to the overall prevalence of HPV positivity. (46) However, the natural history of anal HPV-associated cancers is not as clear as cervical cancers from a precursor perspective. Secondary prevention of anal cancer through screening is a controversial topic. There are no large population-based studies defining the risk of progression of low-grade anal intraepithelial neoplasia (AIN) to anal cancer. However, there are data demonstrating the oncogenic potential of high-grade AIN.

(32, 59) Studies into the natural history of OPC are hampered by a lack of screening methods or comparable malignant precursor lesions, such as CIN or AIN (Table 1).

(13, 20) A clear understanding of the development of premalignant lesions into invasive carcinoma does not exist for cancers of the head and neck. Evidence is beginning to emerge which indicates similarities as well as differences in the natural history of oral and cervical or anal HPV infection. It is not yet known whether the natural history of oral HPV or whether the risk factors for persistent HPV infection in the oropharynx, differ from those known for cervical and anal HPV infection.

Understanding the prevalence, incidence and persistence of oral HPV infection and whether they differ from other anatomical sites is an important epidemiological question. Such knowledge will strengthen the understanding of the natural history of oral HPV infection and its potential malignant sequelae. Outcomes from a large cross-sectional study conducted as part of the National Health and Nutrition Examination Survey (NHANES) reported the prevalence of cervical HPV infection in females aged 14-59 to be six-fold higher than the prevalence of oral HPV infection in men and women aged 14-69 (42.5% and 6.9% respectively). (36, 41) Similarly, studies which aim to compare the prevalence of oral HPV infection and HPV infection at cervical, or other anogenital sites, have shown the prevalence of oral HPV infection to be significantly lower than that of cervical (1, 11, 23, 28, 61, 83), anal (6, 61, 71, 83, 86, 97), or penile (86, 97) HPV infection (Table 2). The higher incidence and persistence of cervical and anal versus oral HPV infections may contribute to the higher burden of anal and cervical HPV-associated as compared to oral cancers.

The overall prevalence rate of oral HPV in the general population has been estimated to range between 1.8% and 7.5% (Table 3a). (29, 36, 56, 57, 64, 68, 73, 80) A recent systematic review by Kreimer *et al.* (54) reported the pooled prevalence of oral HPV infection in cancer-free, HIV-negative subjects from 18 published studies to be 4.5%. The pooled prevalence for oral oncogenic HPV and oral HPV-16 were 3.5% and 1.3%, respectively. (54) Prevalence rates for populations at risk and immunocompromised, human immunodeficiency virus (HIV)-positive populations are considerably higher, ranging from 7.6% to 67% (Table 3b and 3c). (1, 6, 7, 9, 11, 19, 23, 24, 28, 31, 51, 61, 65, 71, 74, 75, 83, 88, 94, 97) A large, comprehensive, meta-analysis published in 2014, of diverse subjects, states a pooled prevalence of 16.9%. (81) Estimates of oral HPV prevalence likely vary due to factors such as varied methods of sample collection, DNA detection assays, number of HPV types tested and subject characteristics.

Fewer studies have reported on the incidence and persistence rates than on the prevalence rates of oral HPV infection in the general population. With regards to incidence, in the first 12 months of follow-up in a cohort of 1626 healthy men aged 18-73 years, Kreimer *et al.* (53) found that 4.4% of subjects acquired oral HPV infections, 1.7% acquired oral oncogenic HPV infection, while 0.6% acquired an oral HPV-16 infection. Other recently published studies have presented comparable results. (29, 73)

Persistence is the detection of the same HPV genotype two or more times over a certain period of time; there is, however, a lack of consensus concerning the length of time necessary to categorize an infection as persistent. (39) This lack of

agreement can lead to inconsistency in the interpretation of the results among various studies. (39) A period of six months to 1 year is the time frame that is most commonly chosen (46) The persistence of high-risk HPV infections is the greatest risk factor for malignant transformation. (26, 46, 53, 74, 91) Of those who have been exposed to and have acquired an HPV infection, most will clear the virus through their own natural immune system, and hence clearance of the virus is more common than persistence. (46, 53) Although lower incidences of oral HPV are observed as compared to cervical HPV infection, similar rates of persistence have been found. (23) Kreimer *et al.* (53) found that in terms of persistence, the median duration of infection was 6.9 months for any oral HPV, 6.3 months for any high-risk type oral HPV, and 7.3 months for oral HPV-16. Eight out of 18 oral HPV-16 infections in this study persisted for more than 18 months. Similar results were found in other recent studies. (29, 73) Based on the available data, it appears that newly acquired oral high-risk, oncogenic oral HPV infections in healthy adults are rare, and most are cleared within one year. On the other hand, a Finnish six-year follow-up study of 324 pregnant women, reported 35.5% baseline HPV-negative women acquired new oral HPV infections, and only 24% of those women cleared the infection. HPV16 and HPV6 were the two most common to persist (76% and 9%, respectively) for a mean duration of 18.6 and 20.2 months respectively. (58)

Some studies are reporting intermittent oral HPV detection within individuals. (6) Presently, it is unclear as to whether intermittent detection is demonstrative of newly acquired infection (incidence), reactivation of a latent infection or the insensitivity of the test used to screen the samples. Furthermore, the palatine tonsils

consist of 10–30 crypts. It has been speculated that HPV-associated tonsillar squamous cell carcinoma arises from the epithelium of the crypts. (90) It is questionable whether the brushings or rinse/gargles, which are commonly used for oral HPV detection, can reach the crypt area.

This evidence demonstrates an effect of anatomic site on the natural history of HPV infection. There are several factors that may influence or contribute to the potentially lower burden of HPV infection at the oral site. Frequency of sexual contact may vary between anatomical sites. The infection of basal epithelial cells is necessary for HPV replication. It is suggested that the virus gains access to these cells through microtrauma or abrasions that expose the basement membrane. Some anatomical sites, such as the anal region, may possess a greater susceptibility to epithelial microtrauma, which provides access to the basal epithelial layer. (6) The oral cavity also possesses local immunity differences, including the continuous flow of saliva that functions to prevent the attachment of viruses and bacteria to the epithelial surfaces. (6) Mucosal transitional junctions are subject to metaplastic conversions associated with chronic inflammation. (43) With respect to the oropharynx, transitional epithelium has been found to be present at the junction of the epipharynx and oropharynx, in islets along the lateral and dorsal walls, and in tonsillar tissue where squamous epithelial tissue transitions into lymphoid type tissues within the tonsillar crypts. (66) Accordingly, these sites may be at increased susceptibility to HPV infections.

A systematic review of studies through September 2010, which calculated pooled risk estimates for the association of HPV with oral squamous cell carcinoma

(OSCC) and oral potentially malignant disorders (OPMD) when compared with healthy oral mucosa as controls, reported that a significant association was found between HPV-DNA detection and both OSCC and OPMD. A subcategory breakdown of OPMD revealed HPV to be associated specifically with oral leukoplakia, oral lichen planus, and epithelial dysplasia. (91)

In summary, oral HPV infection is recognized as a leading cause of a distinct subset of OPC that is rising dramatically in incidence. Establishing the risk factors associated with high-risk oral HPV infection and HPV-positive OPC will not only aid in the establishing the natural history of the disease, but will also identify populations at risk.

Risk Factors

Sex

Epidemiological studies have shown that men have a higher incidence of HPV-positive OPC than women. (5, 16, 22, 49, 100) Several case-control studies designed to evaluate the associations between HPV infection and OPC report a significantly higher incidence in males. (3, 25, 26, 37) These results are consistent with a large meta-analysis performed by Jayaprakash *et al.* (43), which found that the odds of detection of HPV-16 or HPV-18 in the oral cavity in males was twice that of females (OR 2.44; 95% CI, 1.26–4.74%; $p=0.008$). (47)

Likewise, men have been shown to have a significantly higher prevalence than women for oral HPV infection. (6, 22, 36) Men are approximately seven times more likely than women to have an oral HPV infection and about five times as likely to have OPC. (22) However, a lack of association with gender was noted in a South

African study as well as a recent systematic review, where the prevalence of oral HPV was noted to be similar between men and women. (54, 99) One study, conversely, found a higher prevalence of oral HPV in women (18.2%) than in men (4.5%). (33)

It is not well understood why the incidence of HPV-related OPC dominates in men. Whether the higher rates of HPV-associated OPC in men can be accounted for by differences in risk behaviours or biological differences in viral clearance are important questions that remain to be investigated. The influence of sex hormones on the immune system could potentially play a role in viral acquisition and clearance. Higher cervical prevalence of HPV compared to penile prevalence might increase the possibility of HPV infection when performing oral sex on a woman, as compared to performing oral sex on a man, which may account, in part, for the higher rate of HPV-associated OPC in men. Further investigation is required to understand why the disease arises predominantly in men, and whether the natural history of oral HPV infection differs between the sexes.

Age

With respect to age, in a study conducted as part of the NHANES 2003-2006, Hariri *et al.* (41) found that the prevalence of genital HPV infection in women peaked at 20-24 years of age, and declined thereafter. These findings contrast with those of the 2009-2010 NHANES study of the prevalence of oral HPV infection as reported by Gillison *et al.* (20), who found that oral HPV infection followed a bimodal pattern; prevalence was highest in individuals aged 30 to 34 years and 60 to 64 years. This bimodal age pattern was especially evident in high-risk infections. (36)

Other recent epidemiological studies have shown that increasing age is significantly associated with oral HPV infection. (36, 56, 65) There has been discussion whether this may be attributed to an age-related loss of immunity. On the other hand a large, multi-national study showed that the risk of acquisition of oral HPV was constant across age groups. (53)

The average age of diagnosis for OPC is 61 years in women, and 58 years in men. (16) The median age of diagnosis for anal cancer is 60 years in women, and 56 years in men. (6) In contrast, cervical cancer is diagnosed at a younger age than other HPV-associated cancers; the median age of diagnosis for cervical cancer is 48 years of age. (48) One of the established risk factors for HPV-negative HNSCC includes older age (median 62 years). (16, 17) With the emergence of a new subset of HPV-positive OPC, some studies have suggested that people with HPV-positive tumours tend to be younger than those with HPV-negative tumours. A large study by Chaturvedi *et al.* (16) used data from nine Surveillance, Epidemiology, and End Results (SEER) program registries in the US (1973 to 2004; n=17,625), to explore incidence trends for HPV-related and HPV-unrelated oral squamous cell carcinomas. The mean ages for HPV-related OSCCs were diagnosed at younger ages than HPV-unrelated OSCCs (61.0 and 63.8 years, respectively; $p < .001$). (16) Overall, the proportion of OPC arising from sites typically associated with HPV, tend to be diagnosed at significantly younger ages than non-HPV-associated oral cancers. (5, 16, 67)

Tobacco

While HPV-negative OCC and OPC have been significantly associated with tobacco and alcohol consumption, their HPV-positive counterparts have been documented in increasing frequency in the absence of smoking and alcohol use. Studies that examine the role of smoking in HPV-related OPC are reporting varied results. While some studies report that HPV-positive OPC subjects are more likely to be never smokers, (3, 95) other studies are finding no significant differences in terms of smoking between HPV-positive and HPV-negative OPC patients. (14, 26, 37) A recent NHANES study found that the prevalence of oral HPV-16 infection was greater in current tobacco users, compared with never or former smokers. (31) Although a high proportion of individuals with HPV-positive tumours are non-smokers, many have a history of tobacco use. HPV-positive HNSCCs are also recorded in heavy tobacco users. (3, 26, 89) These findings highlight the fact that HPV-associated malignancies not only arise in people who do not smoke, but also occur in people with the traditional risk factor of tobacco use.

One study found that smoking increased the risk of high-risk oral HPV persistence, which is a key event in the progression of HPV lesions. (50) This suggests that smoking may be an indirect risk factor for persistence of HPV oral lesions, and hence their progression to cancerous lesions. Furthermore, this association has been shown to increase with smoking intensity. (36)

Although the independent association between smoking and HPV-positive OPC remains debatable, the prevalence of oral HPV infection has been clearly shown to be significantly associated with cigarette smoking. (23, 36, 53, 56, 75) HPV-positive OPC arises in both the absence and the presence of tobacco; while

tobacco may contribute to the persistence of the infection, tobacco is not shown to be a causative risk factor for HPV-positive OPC.

Marijuana

There exists an association between HPV-positive HNSCC and marijuana use; however, the evidence behind this association is tenuous and mixed. One case-control study out of Baltimore, Maryland, found that HPV16–positive HNSCC was independently associated with exposure to marijuana. In this study, the odds ratios for HPV16–positive HNSCC increased with increasing intensity and duration of marijuana use. (37) It is biologically plausible that marijuana may act to promote the development of HPV-positive HNSCC. Cannabinoids in marijuana smoke can modify the antitumor immune response by binding to the CB2 receptors expressed on natural killer cells, macrophages, dendritic cells, B-lymphocytes and T-lymphocytes found in human tonsillar tissue. (37) This results in suppressed humoral and cell-mediated immune responses, reduced host cell resistance to pathogens, and possibly suppression of antitumor immunity. (36, 37) It is, therefore, arguable that cannabinoids may promote the progression of HPV-positive HNSCC on multiple levels, including but not limited to increasing the risk of infection upon exposure, promoting the persistence of the infection, and inhibiting antitumor immunity. (36, 37) A pooled analysis from Marks *et al.* (62), presents mixed results regarding the association of marijuana use with an elevated risk of head and neck cancer. Data from nine case-control studies show a significantly elevated risk of oropharyngeal cancer among those with higher frequency and longer duration of marijuana use. On the other hand, these findings contrast with those from a review of five previous

studies showing no association. (62) Gillison *et al.* (37) also conclude that no association was found between marijuana use and HNSCC in a California cohort study, nor in several earlier case–control studies.

High-risk sexual behaviour

The sexual transmission of oncogenic HPV types has been demonstrated in cervical cancer and anal cancer. (46) Current epidemiologic evidence suggests that certain high-risk sexual behaviours are associated with the transmission of oncogenic HPV to the oral cavity, which may develop into oropharyngeal neoplasia. Research carried out by D'Souza *et al.* shows an oral HPV increase in couples that practice oral sex.(23, 25)However, another study by the same author, shows that a high prevalence of HPV-16 DNA in HPV-OPC patients is not observed in their partners. (24)These findings suggest that either oral-oral transmission is rare or most partners clear the active infections to which they are exposed.

Recent cross-sectional studies demonstrate that the odds of oral HPV infection are independently associated with the number of lifetime oral sexual partners (22, 25, 36, 57, 73)and the number of recent oral sexual partners. (7, 25, 29, 36, 57)Other studies have shown no significant association between oral sexual contact and the acquisition of high-risk oral HPV infection. (53, 54) When considering these studies that do not show an association with oral sex, it is important to note the potential limitation of recall bias.

It is also important to consider the differing sexual behaviors associated with different ages. For example, D'Souza *et al.* (22), examined sexual behaviors by age group and found that seniors (60-69 years of age) had the oldest age at sexual

debut, and were less likely to engage in oral sex or to have had numerous sexual partners compared to younger age groups.

In addition to oral-genital contact, oral-anal contact was also shown to be associated with oral HPV prevalence.(7)Several studies also demonstrated significant associations between oral HPV and open-mouthed kissing. (25, 73, 75) The presence and the persistence of an oral high-risk HPV infection have been associated with an increase in the risk of persistent oral HPV infection in the subject's partners. (76) In one case, a husband and wife were diagnosed synchronously with HPV16-positive tonsillar cancer. Both viral genomes were genetically identical, with an uncommon signal variant nucleotide being identified in both genomes. Instances such as these clearly represent transmission between the couple. (40)

Similar risk factors have been established in men-who-have-sex-with-men (MSM). Lifetime number of partners (65, 75), number of recent oral sex partners (65), recent oral-anal contact (29, 42, 65), and open-mouthed kissing (75) are significantly associated with high-risk oral HPV infection. Although MSM have a higher prevalence, incidence and persistence of anal HPV-infection than heterosexual men or women (65, 97), the same has not been clearly shown, thus far, for oral HPV-infection. Interestingly, another study evaluating the natural history of anal versus oral HPV infection in HIV-infected individuals noted that MSM had the highest incidence of anal HPV, whereas heterosexual men had the highest incidence of oral HPV. (6) However, data in the natural history study by Videla *et al.* (97) showed only a slightly higher prevalence and a lower clearance rate of oral HPV

infection in the heterosexual group versus the MSM group, and did not reach statistical significance. Furthermore, incidence of oral HPV infection was similar in both groups. (97) Other studies have published prevalence rates for oral HPV-infection and high-risk oral HPV-infection in MSM that are similar to those published in other studies of heterosexual men. (65, 71, 75) At this time, although MSM have shown the highest risk of anal HPV infection, heterosexual men also show a high prevalence of anal HPV infection and a risk similar to that of MSM for penile and oral HPV infection. (97) A cross-sectional study by Beachler *et al.* (7) found that HIV-positive and HIV-negative participants had differing sexual behaviour risk factors for prevalent oral HPV. (7) Among HIV-negative individuals, a higher number of recent oral sex or oral-anal contact were strong risk factors. In contrast, the higher number of lifetime sexual partners was the strongest risk factor among HIV-positive individuals. On the other hand, at least one recent prospective study in HIV-positive individuals has reported no independent significant association between oral sexual behaviours and oral HPV prevalence. (6)

Studies have shown that these high-risk sexual behaviours are not only associated with oral HPV infection, but are also significantly associated with OPC. (26, 42, 92) A pooled analysis of a large case-control study carried out by INHANCE (the Head and Neck Cancer Epidemiology Consortium) with participants from 12 countries, concluded that certain sexual behaviours such as performing oral sex, number of lifetime sexual partners, number of lifetime oral sex partners, age at sexual debut, and history of same-sex or oral–anal contact are associated with

cancer risk of HNSCC subsites, such as the oropharynx, which have previously been associated with HPV infection. (42)

Oral-anogenital concordance

An important question in oral HPV infection is whether it is concomitant with anogenital HPV infection. A site is concordant for HPV when the same genotype of the virus can be detected at both sites. Some studies report that the subjects in their cohort had multiple concurrent infections between sites (6-11%), but the data is not genotype specific. (6, 86, 87, 97) A South African cross-sectional study found that 12% of couples had oral-genital concordance; among these couples the majority was male oral HPV infection, which was concordant with female vaginal HPV infection. (99)

Expanding on the concept of HPV as an infection with potential field cancerization, some studies have examined the relationship between oral and genital or anal HPV infection by evaluating the prevalence rate and type-concordance of HPV infection between these anatomic sites. A recent meta-analysis indicates that there is a type-specific concordance between oral and cervical HPV, and that type-concordance is increased in HIV-positive individuals. (94) Several studies have confirmed that women with genital HPV or anal HPV infection are at higher risk for same type-specific oral HPV infection. (1, 11, 23, 82, 83) Other studies have demonstrated a conflicting conclusion regarding the prevalence of concordance among different HPV types, and lack of or low concordance between anatomical sites. (71, 87, 104) In a study of 129 female participants, in only one case (0.8%), was the same HPV type detected in both the cervix and the oral cavity.

(64) A recent study by Kofoed *et al.* (51), reports that the concordance between anal and genital HPV types is 78.1%, while concordance between oral and genital types is 60.9%, with a lower concordance of 21.7% observed between anal and oral HPV types. In a study of 105 women, all patients with an oral HPV infection also presented with a genital HPV infection. (98) However, this study did not examine the specific genotypes of these infections and hence, concordance between sites could not be determined.

Studies of heterosexual couples have found high rates of transmission and concordance between the couple's genital sites. (76, 101, 102) A similar peak in genotypic concordance was found between oral and genital sites in at least one study. (8) However, a similar peak in concordance was not seen between genital and non-genital anatomic sites in several other small studies. (76, 101, 102)

At least one study has demonstrated that patients with cervical cancer develop increased incidence of second primary cancers of the head and neck compared to females with other cancers. (78) Published case studies show that some individuals who have had HIV infection and who developed HPV-related anal squamous cell carcinoma, later developed oral squamous cell carcinoma. (15) A large US population-based epidemiological study (n = 47,308) tested the hypothesis of a bidirectional association between anogenital and OCC/OPC HPV-associated cancers in men using the SEER cancer database. The standardized incidence ratios were elevated for both anogenital cancer following OCC/OPC and for OCC/OPC following anogenital cancer. The increase was most pronounced for tonsillar cancer following anal cancer. (85)

Together these results suggest a mode of HPV transmission between the oral and genital sites, reinforcing the possibility of sexual transmission of the virus to the oral cavity. Since oral and anal HPV infections have been reported among individuals who reported no recent anal or oral sex, other non-sexual modes of transmission, including self-inoculation, are also possible. (6) Larger, longitudinal studies are necessary to examine the role of HPV infection in anogenital sites and transmission to the oral cavity.

Immunosuppression

Some studies have examined the incidence of cancer in organ transplant recipients. Patients with immune suppression maintained by drugs to prevent rejection of transplanted organs are at a higher risk for virus-related cancers, including HPV-OPC. (60) The extent of immunosuppression varies according to factors such as type of organ transplant, time since transplant, and drug regimen. For example, an increased incidence of OPC has been observed amongst liver recipients as compared with kidney recipients. (60) Additionally, the study found that while the intensity of immunosuppression required based on human leukocyte antigen (HLA) mismatch seemed unlikely to be an important predictor for HPV-related cancers, OPC was the only type of cancer whose incidence increased with the number of HLA mismatches. (60)

Individuals with HIV have a two- to six-fold increase in risk for OCC and OPC relative to the general population. (30, 38, 84) HIV-positive individuals have an increased risk of HPV-positive cancers of the oropharynx (19, 26, 37, 65), as well as other HPV-positive cancers, including cervical, anal, vulvar, vaginal, and penile

cancers. (18, 30, 84) Known potential cervical and anal cancer precursor lesions such as CIN and AIN also occur at higher rates in HIV-positive individuals. (18) The risk of HPV-associated type cancers is elevated among persons with HIV and rises with increasing immunosuppression, consistent with a loss of immunity and reduced control over HPV infections. (18)

A large meta-analysis compared cancer incidence in people with HIV/AIDS and organ transplant recipients. A similar pattern of increased risk of cancer in these populations suggests that an immune deficiency is responsible for the increased risk in HPV-positive cancers, rather than other risk factors such as high-risk sexual behaviour. (38) Infection-associated cancers, including HPV-associated cancers, are becoming an increasingly prevalent complication of long-term HIV infection.

Even after controlling for high-risk sexual behaviour, the prevalence, incidence, and persistence of oral HPV-infection remains significantly elevated in HIV-positive compared to HIV-negative individuals. (6, 7, 9, 21, 31, 65, 75, 97) In healthy men, the collective incidence of HPV-16 is described to be around 0.8 infections per year. In HIV-infected men, however, that incidence rises to 0.8 infections per month in MSM and 2.2 per month in heterosexuals, indicating the greatest risk of oral HPV-16 infection is in HIV-infected heterosexual men. (19) Beachler *et al.* (6), reported an overall prevalence and persistence for oral HPV to be 28% and 29% respectively ($p < 0.001$) in HIV-positive individuals. Videla *et al.* (97) observed similar results in their single-center, prospective cohort study in Barcelona. The prevalence of oral HPV was found to be 16%, incidence was found to be 11%,

and clearance was reported to be 44% in their HIV-positive cohort. (97) In short, HIV-infected individuals appear able to clear many anal and oral HPV infections, but persistent and intermittent infections remain common.

Prevalence of oral HPV is strongly associated with immunosuppression. (7) Current CD4 count is the strongest predictor, and the association between oral HPV-16 and current CD4 was significantly stronger than the association with all other HPV types. (7) These findings are consistent with the presence of a strong, independent association between HIV-related immunosuppression and the burden of oral HPV infection. The higher incidence and persistence of oral HPV infections likely contributes to the higher burden of oral HPV-associated cancers in HIV-infected individuals.

The effect of HAART on oral HPV and HPV-positive OPC

Recent research suggests that highly active antiretroviral therapy (HAART) may not decrease the prevalence of oral HPV. (4, 12, 27) Moreover, since the introduction of HAART, an increase in the frequency of HPV-associated oral lesions, such as squamous cell papilloma, verruca vulgaris, condyloma acuminatum, and multifocal epithelial hyperplasia, has been observed. (4) This contrasts with the reductions seen in other oral lesions seen during the HAART era, such as oral candidiasis, hairy oral leukoplakia, and oral Kaposi's sarcomas. (72) One cross-sectional study shows that a longer duration of HAART use (greater than 12 months) is associated with HPV-oral lesions. (4) Conversely, at least one cross-sectional study has reported that no significant difference in the prevalence of oral HPV16 infection was observed between those who were and were not taking HAART. (2)

HPV-associated oral lesions are not only associated with longer HAART use, but also with older age. The increase of these lesions in older HIV patients who are taking HAART may be related to longer life expectancy of individuals with an impaired immune system, rather than a direct relationship with HAART.

Several studies have shown that the relative hazard of developing anal cancer among HIV-positive individuals is significantly higher in the post-antiretroviral therapy (ART) era compared with the pre-ART era. The trends for OPC over time do not appear to have improved with HAART. (27, 93) Overall, the data indicates a growing risk of HPV-related cancer among HIV-positive individuals since the introduction of HAART, particularly among HIV-positive MSM. (27, 45)

Potential Implications of Vaccination on HPV-associated OCC and OPC

Initial data from post-vaccine randomized clinical trials in Costa Rica and England are indicating that, within 3-4 years of vaccine introduction, oral HPV-16/18 prevalence has decreased among females aged 16-25. (44, 63) Based on these initial findings, the World Health Organization's International Agency for Research on Cancer released a statement suggesting that the vaccine affords protection against vaccine-type HPV oral infection, with potentially significant implications for the prevention of HPV-associated OPC. (103) Verifying a decline in oral cancer rates in the setting of HPV vaccine trials would provide some of the strongest possible causal evidence for a temporal relationship between oral HPV infection and the development of oral malignancy. (52, 63, 77)

There is strong evidence to indicate the positive impact of HPV vaccination in females. The possibility of an extension of the vaccine to the male population is

worth exploring, as this population has also been identified to be at risk for anal, genital and oropharyngeal cancers.(81)

CONCLUSION

The overall incidence of HPV-related OPC continues to increase, highlighting the need to understand the natural history and etiology of oral HPV infections causing these cancers. While the natural history of oral HPV infection is not fully understood, it appears that newly acquired high-risk, oncogenic oral HPV infections in healthy adults are rare and while most are cleared within one year, some may persist in a subset of infected individuals. At this time, evidence demonstrates that men have a significantly higher prevalence than women for oral HPV infection. Age, immune status, number of sexual partners, and certain types of sexual contact are significantly associated with a higher risk of oral HPV infection.

HPV-associated OPC represents a distinct clinical and biological entity, with many unanswered questions that should be explored in future translational, scientific research. There is a need to further investigate why the disease arises disproportionately in men, and whether the natural history and etiology of oral HPV infection differs between men and women. Risk factors need to be ascertained. Further studies are necessary to examine the role of HPV infection in anogenital sites and transmission to the oral cavity. Studies designed with appropriate risk stratification will lead the identification of the highest risk groups who can then be targeted for prevention and screening of the potential malignant sequelae of oral HPV infection. Larger, longitudinal studies with extended follow-up will further the understanding of the natural history of oral HPV as well as the potential impact of

screening and prophylactic HPV vaccines, particularly for populations which have been established as being at-risk for HPV-associated OPC.

High-risk oral HPV infection is emerging as causal risk factor for OPC. The incidence of OPC is rising, and clinicians should be aware of the established risk factors and identified populations at risk. Early vaccination against high-risk HPV is important, especially for populations that have been identified to be at risk. These at-risk populations include both young girls, as well as boys.

CONFLICT OF INTEREST

The authors declare that there was no funding for this review and no conflict of interest.